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Stress echocardiography testing: Is submaximal good enough?

Michael W. Fong and John C. Teeters

University of Rochester Medical Center, Rochester, New York, USA

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Exercise and pharmacologic stress echocardiography have been used routinely in clinical practice for the past twenty to thirty years [1–3]. Over this time, stress echocardiography has become an accepted means of evaluation for perfusion-limiting coronary artery obstruction, and for assessing risk. Historically, based on meta-analyses, the sensitivity and specificity have been reported to be approximately 80% [4, 5]. However, it has been traditionally held that exercise stress testing is superior to pharmacologic stress testing due to a more "physiologic" effect with exercise.

A limitation of any exercise stress testing modality has been that patients must achieve a target heart rate of 85% of their maximal predicted heart rate (calculated as 220 – patient's age) for the study to be considered "diagnostic" [6]. Recent data have challenged traditional thinking by demonstrating superiority of the dobutamine stress protocol over standard exercise stress echocardiography, with a nearly four-fold higher likelihood of achieving target heart rate [7]. Given the increase in the number of patients on rate-lowering beta and calcium channel blocking agents, especially amongst those with known ischemic heart disease, the diagnostic utility of stress testing has become an important issue. Since these medications are more likely to blunt the chronotropic response, yielding submaximal heart rates, studies may often be rendered inconclusive.

Among patients not on heart rate lowering agents, the rate of failure to reach at least 85% of the maximal predicted heart rate is 15–25% [8]. Amongst those on beta-blockers, the reported incidence of failure reaches 30–50% [9, 10]. The inability to reach target heart rate has been termed "chronotropic incompetence", and is predictive of cardiac death, independent of abnormalities on stress testing or other comorbid illnesses [8]. The administration of atropine has become a common component of pharmacologic stress protocols in order to overcome submaximal stress, and help patients achieve target heart rates [10]. While the use of atropine has been demonstrated to increase the overall sensitivity of dobutamine stress echocardiography (DSE), it is achieved at the expense of other useful information such as heart rate recovery and the presence of chronotropic incompetence [8, 10]. These findings have great prognostic implications; thus, while a useful tool to improve heart rate response and demonstrate wall motion abnormalities on echocardiography at peak stress, key information may be lost with the use of atropine.

The true diagnostic utility of submaximal stress testing, particularly in patients on heart rate lowering agents, has not been well studied and is not well understood [11]. Although there is evidence that dobutamine may be more efficacious in helping patients to achieve target heart rates [7], there is still considerable controversy as to the predictive value of these tests if maximal predicted heart rate is not attained. In this edition of the "Cardiology Journal", Patel et al. [12] attempt to answer this question by presenting an interesting study examining the prognostic capability of DSE with submaximal heart rate response. The study looks retrospectively at 756 patients with negative DSE testing, divided into two groups based on the achievement or failure to achieve a maximal predicted heart rate ≥ 85%. Not surprisingly, beta-blocker and calcium channel blocker usage was higher in the group that did not achieve target heart rate. The striking finding in this study is that the traditional combined outcome of cardiac

Address for correspondence: Michael W. Fong, MD, University of Rochester Medical Center, 601 Elmwood Avenue, Box 679-T, Rochester, New York 14642, USA, e-mail: Michael_Fong@urmc.rochester.edu

death, nonfatal myocardial infarction, and revascularization was not significantly different between those who had submaximal heart rate thresholds, and those who achieved a maximal heart rate response after a mean of 36 months of follow up. The authors report a three year event-free survival of 98% in both groups.

The study seems to suggest that negative submaximal DSE may be an acceptable predictor of future risk, particularly in patients on nodal blocking agents. The one caveat to this finding is diabetes, which on multivariate analysis was found to be a significant predictor of any cardiac event. Examining the study more closely, the relative youth of the submaximal heart rate group (69.4 ± 12.9 *vs.* 73 ± 11.1 years of age, $p < 0.0001$) is a confounding variable that may confer an event-free survival benefit. However, this group also had a higher incidence of prior PCI (with a notable trend towards an increase in prior myocardial infarction, $p = 0.08$), hypertension, history of heart failure, and diabetes, all of which would be expected to increase the number of adverse cardiac events. In any case, the other important factor that must be considered when interpreting the study is that more than 80% of the patients had a normal left ventricular ejection fraction; which speaks to the overall health of the group. Whether or not the results would be reproducible in a group with underlying resting systolic dysfunction is unknown, and certainly, future studies examining this subgroup would be useful.

The current study by Patel et al. [12] builds upon a previous study by Labib et al. [13] from 2004 which demonstrated non-differential cardiac event rates among 429 patients with negative maximal and submaximal DSE prior to non-cardiac surgery. Further, Patel et al. [12] reaffirmed the finding that diabetic patients with a negative stress echocardiogram are at a significantly higher risk of cardiac events than their non-diabetic counterparts, as previously shown by Kamalesh et al. [14] (19% incidence of cardiac events amongst diabetics versus 9.7% amongst non-diabetics). Thus, one must still use caution in taking reassurance in a negative stress echocardiogram in this population.

In conclusion, DSE remains a clinically valid and useful tool for stratifying patients' future risk of cardiac events. The study by Patel et al. [12] does provide evidence for the prognostic utility of negative submaximal DSE, particularly amongst patients on heart rate lowering medications. However, interpretive restraint must be used amongst diabetic patient's as there is still a significant risk of adverse cardiac events in this population. Future studies examining the usefulness of negative submaximal DSE testing in patients with underlying systolic dysfunction are needed, as the current study was not intended to, and does not adequately assess, this population.

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